Statement
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The Role of NIH-Supported Research in the Response to 2009 H1N1 Influenza

Statement of

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Mr. Chairman and members of the Subcommittee, thank you for the opportunity to discuss the NIH research response to the pandemic caused by the novel 2009 H1N1 influenza A virus, which the President declared to be a National Emergency on October 24, 2009.

Over the past several years, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) within the U.S. Department of Health and Human Services (HHS), has conducted a major research effort that builds on long-standing programs related to seasonal influenza in order to improve our preparedness for pandemic influenza. Although in this decade we have focused a good deal of attention on H5N1 avian influenza, it always has been clear that the next pandemic threat could come from another influenza virus altogether.

The new pandemic influenza virus is now here and is widely spreading throughout the globe. In response, NIH has intensified the implementation of the research agenda that underpins the development of countermeasures for all influenza subtypes, and in particular, the 2009 H1N1 virus.

In my remarks today, I will discuss the research response being mounted by NIH that is complementary to—and synergistic with—the efforts of other components of HHS such as the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and

Response, and our sister agencies, the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), as well as other organizations throughout the world.

Seasonal and Pandemic Influenza

Influenza viruses affect many animal species, including birds, pigs, and humans. As influenza viruses circulate, the genes that determine the structure of their surface proteins undergo small changes called mutations. These genetic changes accumulate over time to cause a gradual "antigenic drift" that allows an influenza virus in a typical influenza season to largely evade the preexisting immunity that a significant proportion of the population may have developed from prior exposure to influenza viruses or from prior vaccinations. Antigenic drift in human influenza viruses is the basis for the predictable patterns of seasonal influenza seen in most years and is the reason that we annually reassess and frequently change the strains to be included in the seasonal influenza vaccine.

In humans, seasonal influenza epidemics in the Northern hemisphere usually occur in winter months. According to the CDC, these seasonal events cause symptomatic illness in 15 to 60 million people in the United States every year; they result in an average of approximately 200,000 hospitalizations and 36,000 deaths. Residual or background immunity from prior exposure to related influenza viruses or from prior immunizations tempers the number of illnesses, hospitalizations, and deaths we see each year. Most of the severe outcomes

from seasonal influenza occur among people aged 65 years and older, in very young children, and in those with chronic health conditions. Globally, seasonal influenza causes 3 million to 5 million cases of severe illness each year, and an estimated 250,000 to 500,000 influenza-related deaths, according to the World Health Organization.

Influenza viruses also can switch hosts, from an animal source to humans, which can pose a more serious threat to human health. One way this could occur is through the infection of humans by a novel influenza virus from a non-human source. For example, influenza viruses infecting birds can, on rare occasions, also infect humans. Although the result is usually a "dead-end" infection that does not spread further, the virus might undergo mutations that allow limited human-to-human transmission. Once transmission begins, further mutation can make human-to-human transmission more efficient and sustainable. Another way that a novel influenza virus can circulate in humans is "antigenic shift" that occur through a process called reassortment, in which two virus strains co-infect a host and exchange genes resulting in a hybrid virus. Whatever the mechanism, the result may be the evolution of a new virus to which the human population has little or no immunity. If this new virus is able to efficiently transmit from human to human, then an influenza pandemic may result. An influenza pandemic is an unpredictable and rare event that can occur at any time of year.

In the 20th century, influenza pandemics occurred three times—in 1918, 1957, and 1968. The pandemics of 1957 and 1968 were serious infectious disease events that killed approximately two million and 700,000 people worldwide, respectively. The 1918-1919 pandemic, however, was catastrophic: epidemiologists estimate that it killed more than 50 million people worldwide, including more than 500,000 people in the United States, and caused enormous social and economic disruption.

Given this history, we long have expected that a new influenza virus would emerge and another pandemic would occur. Since the initial spring outbreak of a novel influenza strain, the 2009 H1N1 influenza virus, this virus has triggered a worldwide pandemic and emerged as the dominant influenza strain in the Southern hemisphere during its winter influenza season. Here in the United States, we continued to see influenza activity over the summer, which is totally unlike the pattern with typical seasonal influenza. More recently, we have seen a marked increase in 2009 H1N1 influenza activity in most states associated with the return of students to school, a trend we expect will continue in the coming months.

The U.S. Government, and HHS in particular, has been preparing for an influenza pandemic for many years. These efforts were bolstered after H5N1 avian influenza reemerged in Southeast Asia in 2003. U.S. Government pandemic preparedness plans assign to the NIH the primary responsibility for

scientific research and clinical trials needed to develop and test pandemic influenza vaccines and therapies.

For decades, NIH has supported basic influenza research to understand better how influenza viruses replicate, interact with their hosts, stimulate and evade immune responses, and evolve into new strains. Results from these basic research studies lay the foundation for the design of new therapies, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike. NIH has worked with FDA and our partners at academic medical centers and in the biotechnology and pharmaceutical industries to speed development of new influenza vaccines, diagnostic tools, and anti-influenza drugs. We also have built a substantial infrastructure of research centers, NIH intramural and NIH-supported extramural laboratories, highly trained personnel, and clinical research networks to rapidly conduct research should a virus with pandemic potential emerge.

NIH is presently engaged in an accelerated effort to fully understand the currently circulating 2009 H1N1 influenza virus and to rapidly develop effective countermeasures. Scientists already have learned a great deal about the biology of the 2009 H1N1 virus, and we are taking numerous steps to learn more. NIH also has been fulfilling its role in developing vaccines and testing therapeutics to counter this newly emerged virus.

Basic Science

When the emergence of 2009 H1N1 influenza was first reported, scientists at CDC, FDA, NIH, NIH-supported laboratories, and elsewhere around the world obtained samples of the 2009 H1N1 virus. NIH immediately began a thorough and rapid characterization of the virus in cell culture and laboratory animals, as well as genetic and structural studies of the virus. That effort involved intramural researchers on the NIH campus, researchers in preexisting NIH research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as industry partners and individual NIH grantees.

These efforts already are yielding important information about the virus. For example, NIH-supported CEIRS researchers have found that the novel 2009 H1N1 influenza virus may have a biological advantage over seasonal influenza viruses in animal models. Preliminary findings in ferrets suggest that the levels of 2009 H1N1 influenza virus rise more quickly than seasonal influenza virus strains and that the 2009 H1N1 virus causes more severe disease. We expect that NIH-supported research will continue to provide critical insights into the mechanisms by which the virus causes disease, its molecular signatures of virulence and enhanced transmission, and the major viral and host factors important in mounting an immune response to the virus. NIH-supported researchers also are implementing a number of clinical studies to provide crucial

information about how the virus behaves in humans, how the human immune system responds to it, and how much cross-protection, if any, is provided by antibodies to previously circulating human H1N1 viruses.

Vaccines

Working with its partners in industry and academia, HHS agencies such as NIH, CDC and FDA have completed key steps in the development of vaccines for the 2009 H1N1 influenza—we have characterized the virus, identified a candidate strain, expedited manufacturing, and conducted clinical trials. HHS has contracted to purchase vaccine from five vaccine manufacturers who are producing either inactivated or live, attenuated H1N1 influenza vaccines by the same methods that are used annually for the production of seasonal influenza vaccines. The 2009 H1N1 vaccines from four of these manufacturers were approved by the FDA on September 15, 2009, for use in the United States. Inactivated vaccines are based on chemically killed influenza viruses and are injected intramuscularly, whereas live, attenuated vaccines are based on a weakened influenza virus and are administered as a nasal spray. The first lots of the 2009 H1N1 influenza vaccines became available in early October.

NIH has used its longstanding vaccine clinical trials infrastructure—notably our network of Vaccine and Treatment Evaluation Units (VTEUs)—to conduct a series of clinical trials to quickly evaluate pilot lots of 2009 H1N1 inactivated vaccines to assess their safety and ability to induce immune responses that are

predictive of protection. Data from these trials have helped to inform the development of recommendations for immunization schedules, including the optimal dosage and number of doses for individuals in different age brackets and for specific groups such as pregnant women. Close collaboration among NIH, FDA, and BARDA was critical in launching these studies quickly while ensuring the usual high standards for the conduct of clinical trials.

Trials to evaluate the safety and immune response of two different dosages (15 micrograms versus 30 micrograms) and one versus two doses of vaccine in healthy adults and the elderly began in the first week of August. As NIH announced on September 11, preliminary data indicate that the vaccines are safe and that a single 15-microgram dose induces what is likely to be a protective immune response in healthy adults between the ages of 18 and 64 years. For adults aged 65 and over, preliminary data indicate that the immune response to the 2009 H1N1 influenza vaccine is somewhat less robust, as is the case with seasonal influenza vaccine. These data are consistent with early data from independent studies conducted by several of the vaccine manufacturers. Complete immune response data from the trials studying two doses in healthy adults are expected in mid- to late November.

NIH is conducting similar trials in populations who are at higher risk of influenza complications, including children, in whom a trial began in mid-August, and in pregnant women, in whom a trial began in September. Early data from the

pediatric trials suggest that one dose of vaccine in older children, aged 10 to 17 years, may be adequate to induce a robust immune response. While we continue to evaluate data from our studies and those of the manufacturers, younger children generally had a less robust early response to just one dose of the vaccine and at this point will require two doses similar to the dosage recommendation for seasonal influenza in this age group.

NIH is conducting additional studies of the vaccines in other populations, including HIV-positive individuals and people with asthma. Two clinical trials to evaluate the 2009 H1N1 influenza vaccine in HIV-infected pregnant women, children, and youth began in October, with preliminary results expected in early 2010. The first patients with asthma were enrolled in a 2009 H1N1 influenza vaccine clinical trial in mid-October. Preliminary results from this trial are expected at the beginning of 2010.

A concurrent set of trials now underway will determine whether the 2009 H1N1 influenza vaccine and seasonal influenza vaccine can be administered at the same time or sequentially and whether both vaccines will induce protective immune responses. These trials are being conducted in healthy adult, elderly, and pediatric volunteers. Early data suggest that these vaccines can be co-administered without negatively impacting the immune response to either vaccine.

Finally, NIH is supporting trials of 2009 H1N1 influenza vaccines that contain adjuvants. Adjuvants are additives that help create a more vigorous immune response to a vaccine, thereby reducing the amount of antigen required per vaccine dose. Currently, it is not expected that adjuvants will be used in a U.S. vaccination program against 2009 H1N1 influenza. However, clinical trials are being conducted with adjuvanted vaccines as a contingency plan; an adjuvanted product might be needed, for example, if the virus mutates to become different from the vaccine virus, if certain populations do not mount an adequate immune response to vaccination, or if we need a larger supply of vaccine. The first adjuvant trial began in late September, with the first preliminary immune response data expected in mid-November.

NIH and its industry partners have been developing several other kinds of influenza technologies and vaccines that are not yet licensed for use. These include recombinant DNA technologies that yield subunit vaccines, in which various influenza virus proteins are selectively produced in cultured cells and are then purified and used in a vaccine; DNA vaccines, in which influenza genetic sequences are injected directly into a person to stimulate an immune response against the proteins coded for by these genetic sequences; and approaches that insert the genes of influenza virus into a different virus (a "vector") that is used as a vaccine. For example, a study of a prototype 2009 H1N1 influenza vaccine that relies on one of these experimental strategies is underway; the NIAID Vaccine Research Center is enrolling healthy adults in a clinical study of its DNA-

based H1N1 influenza candidate vaccine. In addition, NIAID's effort to support development of a novel purified hemagglutinin vaccine has recently resulted in a BARDA contract to further develop this product. Because such "next-generation" vaccines will require additional safety and efficacy testing before they can be deployed, and because, even if safety and efficacy are proven, scaling up to commercial levels of manufacturing is complex, they will not reach the public during the upcoming influenza season.

Antiviral Therapies and Diagnostics

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza, by treating infection after it occurs and, under certain circumstances, by preventing illness prior to or immediately after exposure. There are three antiviral drugs currently available for treatment of influenza during the H1N1 pandemic. The 2009 H1N1 influenza virus is sensitive to oseltamivir (Tamiflu®) and zanamivir (Relenza®). In addition, an intravenous formulation of peramivir for treatment of hospitalized patients with serious influenza infections was recently authorized by the FDA under Emergency Use Authorization. Unfortunately, resistance to influenza antiviral medications frequently emerges. Indeed, over the past two years the circulating seasonal H1N1 influenza viruses have become widely resistant to oseltamivir, even while other influenza viruses have remained sensitive to the drug. Hence, it is critical to maintain a pipeline of new and improved anti-influenza medications.

In recent years, NIH has been working to develop and test the next generation of influenza antivirals. Three of these drugs are now in clinical testing, including a long-acting neuraminidase inhibitor, an inhibitor of viral replication, and a drug that prevents the virus from entering human lung cells. NIH has begun evaluating how well these candidate antiviral drugs block the 2009 H1N1 strain and screening other compounds for activity against the virus. In this regard, 462 compounds have been tested against the pandemic H1N1 virus, 33 of which showed antiviral activity. NIH intends to conduct clinical trials of antivirals, including new formulations and combinations of licensed drugs and investigational antiviral candidates, in individuals infected with the 2009 H1N1 influenza virus.

Improved methods of diagnosing 2009 H1N1 influenza infection at the point of care would be of substantial value in the months ahead, helping to differentiate people with the new influenza strain from those with other conditions who present with similar symptoms. Prompt and precise point-of-care diagnosis would help to slow the spread of the influenza virus and maximize the efficiency with which stockpiled antivirals are used. NIH has been developing diagnostic platforms capable of rapidly identifying a wide variety of pathogens in clinical samples, including specific subtypes of influenza, and we are now working to accelerate the development of these platforms to provide improved diagnostics for 2009 H1N1 influenza.

Shared Research Resources

When infectious diseases emerge, NIH serves an important role in providing research materials, support, and expertise to scientists and to the public health community. These research resources include blood samples from infected patients, immunological assay reagents, animal models, genomic sequencing and information resources, and isolates of the virus.

NIH intramural and extramural researchers, in turn, depend on materials and information shared by CDC, FDA, and other public health agencies around the world. For example, CDC provided NIH intramural investigators and NIH-supported researchers with samples of the 2009 H1N1 virus, while NIH has made available to CDC researchers archived blood samples from people vaccinated against 1976 swine influenza as well as influenza reagents from an NIH research reagent repository. From my perspective, the coordination and cooperation among government agencies, and with academia and private industry, has been outstanding.

Conclusion

It is important to recognize that, even months into this worldwide pandemic, we are still only at the earliest stages of understanding how the 2009 H1N1 influenza virus emerged and what impact it might have. Influenza viruses are highly unpredictable, and it is unwise to make predictions about how a virus might behave in the future. For example, although the virus has for the most part

caused moderate influenza symptoms (with important and tragic exceptions), we do not know whether that might change in the coming months. Nor do we know whether the virus will become resistant to the antiviral drugs we have stockpiled. In short, we simply cannot predict at this time whether the 2009 H1N1 pandemic will become more or less severe than we have seen thus far. For these reasons, the NIH and other government agencies have been preparing for any possibility.

The ongoing, collective efforts of HHS, including the NIH, to prepare for an influenza pandemic—with surveillance, research, vaccine manufacturing infrastructure and clinical trials, antiviral drugs, public health measures, effective infection control, and clear public communication—have given us a valuable advantage in responding to the current worldwide pandemic, however it may unfold in the future.

I would be pleased to answer any questions you may have.